

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 February 2002 (28.02.2002)

PCT

(10) International Publication Number
WO 02/16671 A1

- (51) International Patent Classification⁷: **C25B 3/04**
- (21) International Application Number: **PCT/EP01/08357**
- (22) International Filing Date: **19 July 2001 (19.07.2001)**
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data:
100 40 402.2 18 August 2000 (18.08.2000) DE
- (71) Applicant: **DEGUSSA AG [DE/DE]; Bennigsenplatz 1, 40474 Düsseldorf (DE).**
- (72) Inventors: **LEHMANN, Thomas; Spessartstrasse 47, 63505 Langenselbold (DE). SCHNEIDER, Rolf; John-Wesley-Strasse 2, 63584 Gründau (DE). WECK-BECKER, Christoph; August-Imhof-Strasse 25, 63584 Gründau-Lieblos (DE). DUNACH, Elisabeth; 580, avenue Loubet, F-06270 Villeneuve Loubet (FR). OLIVERO, Sandra; 64, avenue St. Barthelemy, F-06100 Nice (FR).**
- (81) Designated States (*national*): **AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.**
- (84) Designated States (*regional*): **ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).**
- Published:**
— *with international search report*
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 02/16671 A1

(54) Title: **PROCESS FOR THE PRODUCTION OF 2-HYDROXY-4-METHYLMERCAPTOBUTYRIC ACID**

(57) Abstract: The invention relates to a process for the production of 2-hydroxy-4-methylmercaptobutyric acid (MHA) by electrochemical carboxylation of 3-methylmercapto-propionaldehyde in an undivided electrolytic cell containing a sacrificial anode, in an aprotic solvent in the presence of a supporting electrolyte. Preferred anode/cathode combinations are Mg/Mg and Mg/carbon. MHA is obtainable in a high yield.

Process for the Production of 2-Hydroxy-4-methylmercaptobutyric Acid

The invention relates to a process for the production of 2-hydroxy-4-methylmercaptobutyric acid, referred to below as methionine hydroxy analog or MHA for short, from 3-methylmercaptopropionaldehyde.

2-Hydroxy-4-methylmercaptobutyric acid is used as a feed additive in a similar way to methionine and, owing to the structural similarity, it is therefore known as methionine hydroxy (MHA) analog.

Up to the present, MHA has conventionally been obtained from 3-methylmercaptopropionaldehyde, which, in turn, is obtainable by addition of methyl mercaptan to acrolein, by reaction with hydrogen cyanide and subsequent hydrolysis of the 4-methylmercapto-2-hydroxybutyronitrile formed. The need to use hydrogen cyanide is a disadvantage of this process. Owing to the high toxicity of hydrogen cyanide, outlay on safety must be high for the reaction. Another very great disadvantage is the ammonium salt formed by the introduction of nitrogen and its subsequent hydrolytic cleavage, which is formed stoichiometrically and causes correspondingly high pollution of waste water. There is therefore a need for an HCN-free process for the production of MHA.

Accordingly, the object of the present invention is to provide a novel process for the production of MHA, in which, on the one hand, methylmercaptopropionaldehyde is used as a starting component and, on the other hand, instead of HCN another C₁ building block is to be reacted with methylmercaptopropionaldehyde (MMP).

It is known - cf. EP-A.0 189 120 and G. Silvestri *et al.*, Tetrahedron Letters 1986, 27, 3429-3430 - to react carbon dioxide as a C₁ building block electrochemically with ketones and aldehydes, with α -hydroxycarboxylic acids

being formed. While the electrochemical carboxylation of aromatic ketones generally leads to average to good yields, only moderate yields are achieved in the electrochemical carboxylation of aromatic aldehydes and in the
5 carboxylation of aliphatic aldehydes, indeed, only low yields are achieved. In the process of the documents evaluated above, the electrocarboxylation takes place in an undivided electrolytic cell, which contains a sacrificial anode, in an aprotic solvent, which additionally contains a
10 supporting electrolyte. The low yields and low selectivities of the electrochemical carboxylation of aldehydes, and especially aliphatic aldehydes, that have become known up to the present have, until now, prevented a person skilled in the art from seriously considering this
15 method for an industrial process, such as the electrocarboxylation of 3-methylmercaptopropionaldehyde with CO₂.

Against all expectations, it has now been found that MMP can be carboxylated electrochemically in a high yield. The
20 present invention accordingly provides a process for the production of 2-hydroxy-4-methylmercaptobutyric acid (MHA), which is characterized in that 3-methylmercapto-propionaldehyde (MMP) is electrochemically carboxylated with carbon dioxide in an undivided electrolytic cell
25 containing a sacrificial anode in an aprotic solvent in the presence of a supporting electrolyte at an effective cell voltage and MHA is obtained from the MHA salt formed, which is dissolved and/or suspended in the electrolyte and the cation of which comes from the anode. The subclaims relate
30 to preferred embodiments of the process.

The process according to the invention is carried out in a simple electrolytic cell, which has only a single electrolyte chamber, as understood by the term "undivided".

The figure shows a diagram of an electrolytic cell for
35 carrying out the process according to the invention. The

electrolytic cell 1 comprises a centrally arranged sacrificial anode 2 and a cathode 3 arranged at a distance. The electrolytic cell contains a pipe connection 4 for the introduction of carbon dioxide and, if necessary, a
5 device 7 for stirring the electrolyte 8. Anode and cathode are connected together through a supply point 5 via the current conductors 6.

In the electrocarboxylation of MMP with CO₂ according to the invention, a metal that is soluble under electrolysis
10 conditions is used as the anode. Anode materials are, in particular, aluminum, magnesium, zinc, copper and alloys containing one or more of these metals. Although magnesium was mentioned as an anode material in the process according to EP-A 0 189 120, at the same time its use was not
15 advised, because of electropassivation phenomena which occur after a brief current flow. Surprisingly, it has been found that, contrary to this teaching, magnesium displays particularly high efficacy as an electrode material in the electrocarboxylation of MMP and leads to substantially
20 higher yields than the use of an aluminum anode.

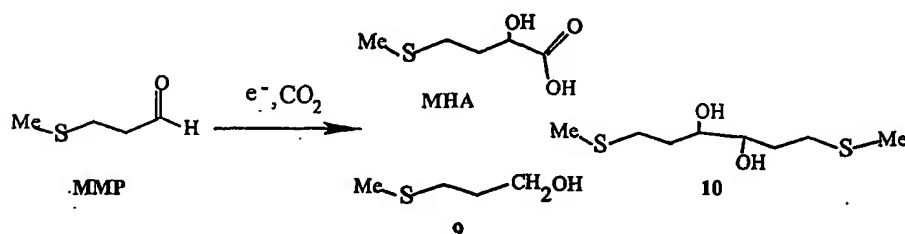
Conventional good conductors are suitable as the cathode. Various conductive carbon materials, such as in particular graphite and carbon fiber non-wovens, are highly suited, as are nickel and especially magnesium. According to
25 particularly preferred embodiments, the anode/cathode combination is Mg/Mg and Mg/carbon, such as in particular graphite non-woven.

The electrochemical carboxylation takes place in an aprotic solvent in the presence of a supporting electrolyte.
30 Suitable solvents are liquid amides, nitriles and open-chain and cyclic ethers. N,N-Dimethylformamide is particularly preferred.

Alkali and alkaline earth halides, ammonium halides, but preferably alkyl, cycloalkyl or aryl ammonium salts,

particularly quaternary ammonium salts, are suitable as supporting electrolytes, it being possible for the residues bonded to the nitrogen to be the same or different and aliphatic, cycloaliphatic or aromatic in nature. The anions of the quaternary ammonium salts are particularly chloride, bromide, iodide, tetrafluoroborate, hexafluorophosphate, para-toluenesulfonate, perchlorate and bis(trifluoromethyl-sulfonimide). Particularly suitable supporting electrolytes are tetra(C₁ to C₄)alkylammonium tetrafluoroborate or hexafluorophosphate.

The formula diagram shows the products formed during the electrolysis of MMP in the presence of CO₂:



- 15 9 = 3-methylmercaptopropanol (MMPol)
 10 = 1,6-bis(methylmercapto)-3,4-hexanediol
 (pinacol derivative, PD)

The following reactions take place during the electrochemical carboxylation of MMP:

- 20 at the anode: $2 M \rightarrow 2 M^{n\oplus} + 2 n e^-$,
 wherein M signifies the anode metal and n the valency;
- at the cathode: $n RCHO + n CO_2 + 2 n e^- \rightarrow n R-CH(O^-)-CO_2^-$
 in the solution: $2 M^{n\oplus} + n R-CH(O^-)-CO_2^- \rightarrow$
 25 $M_2(R-CH(O)-CO_2)_n$
 wherein R denotes $CH_3-S-CH_2-CH_2-$.

The formation of the complex salt prevents the formation of by-products to a fairly large extent. In particular, when

magnesium is used as the anode material, the undesirable formation of pinacol is suppressed, so that the selectivity of the electrochemical carboxylation of MMP is very high. At the same time, when a magnesium anode is used, product
5 yields in the range of around/over 80% are obtainable even without optimizing the process.

To carry out the process according to the invention, MMP is dissolved in the solvent containing a supporting electrolyte and then an effective voltage is applied to the
10 anode and cathode. A voltage in the range of about 3 to 30 V, particularly about 10 to 30 V, has proved favorable; however, a higher or lower voltage is not ruled out. Although a potentiostatic operation is possible, a galvanostatic operation is preferred because it is better
15 for implementation on an industrial scale. The electrolysis is therefore preferably performed galvanostatically with a current density in the range of 0.1 to 10 A/dm², particularly 0.2 to 2 A/dm².

The carboxylation is usefully carried out at a temperature
20 in the range of 10°C to 50°C, particularly 10°C to 30°C. Carbon dioxide can either be introduced into the electrolytic cell with a partial pressure of less than 1 bar in a mixture with another gas, which can, at the same time, serve to improve thorough mixing, or alternatively
25 carbon dioxide is passed through the electrolytic cell under normal pressure. According to another alternative, a CO₂ pressure in the range of 1 to 5 bar is maintained within the electrolytic vessel.

To obtain MHA from the MHA salt dissolved in the
30 electrolyte, this is usefully precipitated out by adding a solvent having low polarity and filtered off. The salt is then treated with aqueous mineral acid by a method that is known per se and the MHA extracted from the aqueous phase by means of an organic solvent, generally having low
35 polarity. The phase containing the aprotic solvent and the

supporting electrolyte is recycled into the electrolysis step after separating off the solvent used to precipitate the MHA salt.

The process according to the invention can be performed in batches or continuously; when operated continuously, a flow-through electrolytic cell is used. The advantages of the process according to the invention lie in the fact that it is possible, using MMP but avoiding the use of hydrogen cyanide, to obtain MHA in a high yield and with good selectivity. In the best current embodiment using a magnesium anode and a magnesium or carbon cathode, tetra-n-butylammonium tetrafluoroborate as the supporting electrolyte and dimethylformamide as the solvent, the methionine hydroxy analog (MHA) is obtainable in a yield of 80% to 85% with a current efficiency of 45% to 60%.

Surprisingly, because contrary to the teaching of the prior art evaluated at the beginning, it has been found that, apart from MMP, other aldehydes, including in particular aliphatic aldehydes such as e.g. phenylpropionaldehyde, can be electrochemically carboxylated in the same way as in the claimed process for the production of MHA with, in some cases, high selectivity, if magnesium is used as the anode. An Mg/C anode/cathode combination is particularly preferred in this case. In addition to quaternary ammonium salts, KCl and KBr are also particularly suitable as the supporting electrolyte. The influence of different supporting electrolytes with the Mg/C electrode pairing in the electrochemical carboxylation of phenylpropionaldehyde to 4-phenyl-2-hydroxybutyric acid (PHBS) can be taken from table 1; the pinacol by-product is 1,6-diphenyl-3,4-dihydroxyhexane. The electrode pairing selected and the supporting electrolyte can also have a marked influence on the yield in the carboxylation of MMP.

Table 1

Supporting electrolyte	Faraday yield, (F/mol)	Conversion (%)	Yield	
			PHBS (%)	Pinacol (%)
$n\text{Bu}_4\text{N}^+\text{BF}_4^-$	5.4	100	50	50
$n\text{Bu}_4\text{N}^+\text{Br}^-$	8.5	75	45	50
KBr	5	34	50	45
KCl	10	55	70	20

The following examples elucidate the invention and show the influence of various parameters on the yield, selectivity and current efficiency.

2-Hydroxy-4-methylmercaptobutyric acid (MHA) was produced by electrochemical carboxylation from 3-methylmercaptopropionaldehyde (MMP).

General Specification

10 The electrolyte is prepared by solutions of the supporting electrolyte (0.025 to 0.1 mol/l) in the electrolyte (N,N-dimethylformamide). Freshly distilled methylmercapto-
 15 propionaldehyde is metered in until the desired concentration is reached. Galvanostatic electrolysis is performed in an undivided electrolytic cell according to the figure with a rod-shaped anode and a sheet-shaped cathode at room temperature. After a specific amount of charge has been consumed, the current is turned off and the solution worked up. For the analytical determination of the
 20 products, esterification is performed with methanol/ H_2SO_4 in the electrolyte solution and a sample is fed into GC analysis. Another method consists in releasing the 2-

hydroxy-4-methylmercaptobutyric acid from its salt by adding acid, and then determining analytically by HPLC.

Example 1

200 µl freshly distilled methylthiopropionaldehyde (= 2
5 mmol MMP) are added to a solution of 50 ml freshly
distilled DMF (N,N-dimethylformamide) and 50 mg
(C₄H₉)₄N(BF₄) (tetrabutylammonium tetrafluoroborate), i.e.
0.15 mmol, as a supporting electrolyte. Electrolysis is
performed in an undivided cell with an Mg sacrificial anode
10 (Mg rod) A = 20 cm² and Mg cathode under ~1 bara CO₂
pressure (atmospheric pressure) at room temperature. The
current applied is 120 mA, i.e. 0.6 A/dm². The cell voltage
varies between 3 and 20 V. After an amount of charge of
960 C has flowed, i.e. 5 F/mol, the current is turned off
15 and the solution worked up. For the analytical
determination of the products, esterification is performed
with MeOH/H₂SO₄ in the electrolyte solution and fed into GC
analysis.

Result: After 90% conversion, MHA is obtained with a
20 selectivity of 75% and with 25% the corresponding
pinacol (PD). A reduction of MMP to methylmercaptopropanol
(MMPol) was not observed here. To work up the reaction
mixture, after acidifying with aqueous HCl the mixture is
extracted with ether and, after evaporating off the latter,
25 the free MHA is obtained.

Examples 2 to 11

The reaction was varied in respect of various parameters.
Table 2 shows the parameters and the results achieved.

The examples show that, with an Mg anode, a higher
30 carboxylation yield can usually be achieved than with an Al
anode.

Table 2

Example No.	2	3	4	5	6	7	8	9	10	11
Anode (area in cm ²)	Al 38	Mg 10	Mg 5	Mg 10	Mg 10	Al 10	Al 10	Mg 10	Mg 10	Mg 10
Cathode (area in cm ²)	Ni 90	C 25	Mg 5	C 25	C 25	Mg 25	Mg 25	Mg 25	Mg 25	Mg 25
Supporting electrolyte (concentration in mol/l)	nBu ₄ NI 0.1	nBuNBF ₄ 0.025	nBuNBF ₄ 0.025	nBuNBF ₄ 0.025	nBuNBF ₄ 0.025	nBuNBF ₄ 0.025	nBuNBF ₄ 0.025	nBuNBF ₄ 0.025	nBuNBF ₄ 0.025	nBuNBF ₄ 0.025
Solvent	ACN	ACN	DMF	DMF	DMF	DMF	DMF	DMF	DMF	DMF
MMP (concentration in mol/l)	0.2	0.05	0.15	*) 0.5 mmol/h	0.05	0.05	0.05	0.05	0.05	0.05
CO ₂ pressure (bara)	1.07	1	4	1	1	1	1	1	1	4
Current density (A/dm ²)	0.6	0.3	1.2	0.24	0.3	0.3	0.3	0.3	0.6	0.3
MHA yield (%)	19	30	85	80	50	30	50	65	75	85
PD yield		70			50	70	50	35	25	
MMPol yield										
Current efficiency (%)	41	30	52	45	20	20	43	40	40	60
Conversion (%)	80	90			100	85	83	80	90	92

*) Continuous addition of MMP (0.5 mmol/h)

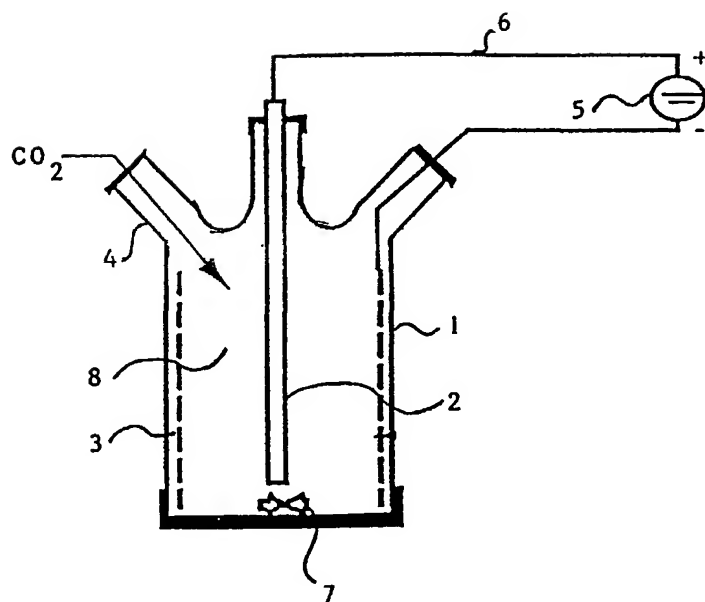
ACN = acetonitrile; DMF = dimethylformamide

PD = pinacol derivative

MMPol = methylmercaptopropanol

What is claimed is:

1. Process for the production of 2-hydroxy-4-methylmercaptobutyric acid (MHA), wherein 3-methylmercaptopropionaldehyde (MMP) is
5 electrochemically carboxylated with carbon dioxide in an undivided electrolytic cell containing a sacrificial anode in an aprotic solvent in the presence of a supporting electrolyte at an effective cell voltage and MHA is obtained from the MHA salt formed, which is
10 dissolved and/or suspended in the electrolyte and the cation of which comes from the anode.
2. Process according to claim 1, wherein the electrochemical carboxylation of MMP is carried out in an electrolytic cell with an anode/cathode combination
15 from the series Mg/Mg and Mg/carbon.
3. Process according to claim 1 or 2, wherein the electrochemical carboxylation of MMP is carried out in dimethylformamide as the solvent in the presence of a supporting electrolyte from the series
20 tetraalkylammonium bromide, tetrafluoroborate or hexafluorophosphate, wherein the alkyl groups in the tetraalkylammonium cation can be the same or different and contain in particular 1 to 4 C atoms.
4. Process according to one of claims 1 to 3, wherein the
25 carboxylation is carried out at a current density in the range of 0.1 A/dm² to 10 A/dm².
5. Process according to one of claims 1 to 4, wherein the carboxylation is carried out under a CO₂ pressure in the range of 1 to 5 bar.
- 30 6. Process according to one of claims 1 to 5, wherein the carboxylation is carried out continuously using a flow-through electrolytic cell.

**Figure 1**

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/08357

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C25B3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C25B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SLAH MCHAREK: "Electrocarboxylation de composés carbonyles aliphatiques, aromatiques et vinyliques: intérêt de l'utilisation d'une anode consommable en magnésium" BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE, 1989, pages 95-97, XP002184312 see whole document	1,3-5
A	US 4 782 173 A (JAMES D. BURRINGTON) 1 November 1988 (1988-11-01) column 1, line 54 - line 68 column 2, line 24 - column 3, line 26	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

29 November 2001

Date of mailing of the international search report

13/12/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Groseiller, P

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/08357

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4782173	A	01-11-1988	BR 8403914 A	09-07-1985
			CA 1251463 A1	21-03-1989
			CA 1275111 A2	09-10-1990
			DE 3462501 D1	09-04-1987
			EP 0133796 A1	06-03-1985
			JP 60100553 A	04-06-1985
			KR 9006447 B1	31-08-1990
			YU 136884 A1	31-10-1986

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.